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10/541,657	03/03/2006	Robert M. Jones	34.US5.PCT	4098

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EXAMINER	
MURRAY, JEFFREY H	
ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
03/09/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/541,657	JONES ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-85,87-92 and 100* is/are pending in the application.

4a) Of the above claim(s) *4-8,10,62-69,71,77,79-85,87-92 and 100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9,11-61,70,72-76 and 78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/7/05* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/1/2007; 9/17/2007; 1/24/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an election from a restriction requirement filed on December 19, 2008. There are ninety-two claims pending and seventy-eight claims under consideration. Claims 86 and 93-99 have been cancelled. Claims 4-8, 10, 62-69, 71, 77, 79-85, 87-92 and 100 have been withdrawn. This is the first action on the merits. The present invention relates to certain 1,2,3-trisubstituted aryl and heteroaryl derivatives that are modulators of glucose metabolism. Accordingly, compounds of the present invention are useful in the prophylaxis or treatment of metabolic disorders and complications thereof, such as, diabetes and obesity.

Election of Group V was made **with** traverse in the reply filed on December 19, 2008. Applicants argue that a) there is unity of invention, and b) if there is not unity of invention, examiner did not properly restrict the application.

Examiner asserted that there was no unity of invention for different reasons. In the restriction requirement it was asserted:

> "The technical feature linking the claims is a compound of general formula I. In the instant case, Groups I-XIII are directed to structurally dissimilar compounds such that the variable core created by varying the definitions of the Formula do not belong to a recognized class of chemical compounds in the art, and references that exist in anticipating one invention would not render obvious the others. For example, 1-[6-(4-Imidazol-1-yl-phenoxy)-5-nitro-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester is different from 1-{4-[2-Nitro-3-(4-propyl-piperidin-1-yl)-phenoxy]-phenyl}-ethanone. Thus, separate searches in the literature would be required. Each group's compounds are made and used independently of each other and could support separate patents. The compounds differ significantly in chemical structures. One skilled in the art would not consider such diverse structures as functional equivalents of each other. The mere fact that there is a single similarity is not in itself a significant reason to render the whole embodiment obvious. Furthermore, the inventions as claimed do not encompass overlapping subject matter

> and there is nothing of record to show them to be obvious variants. Therefore the feature linking the claims does not constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the art."

Applicants argue that there is a special technical feature that links all the compounds. Applicants state:

- A six membered aromatic core ring having carbon atoms at least three adjacent positions (positions 1,2 and 3) and at least a fourth position not adjacent to the first three (position 5).
- An aromatic ring optionally linked by a linking group as a substituent at position 1.
- A substituent at position 2; and, finally A cyclic amine as a substituent at position 3.

Examiner disagrees and notes that there is no special technical feature for this core compound here. The only common portion of ALL the compounds encompassed by the scope of these claims is the central ring, which at best can be a pyrimidine, pyridine or phenyl ring according to the claim set, therefore no unity of invention exists. Examiner asserts that a special technical feature is exactly that, "special." Any position where multiple variables may exist, such as X, Y, Ar_1, the N-A-B-D ring, Z and R_1, then those positions cannot be considered "a special technical feature" if those positions van be represented by multiple different groups in the compound. For a prior art example which reads on the claims and thus breaks the unity of invention please see the 102(b) rejection cited below.

Applicants have additionally argued that if the special technical feature is not present, and hence there is no unity of invention, that the examiner did not properly restrict the claims. Examiner points to the restriction requirement and notes that there

are groups for every possible scenario of compound for the claims set forth in the claim set. Applicants also argue that the restriction requirement abridges their right to claim the generic subject matter. Applicant is correct. This is because the generic subject matter was deemed to be multiple inventions. Applicants may not claim subject matter so generic that it results in multiple patentable inventions.

Finally, as a matter of form, examiner would like to remind applicants that the election of a species is merely to denote a starting point in the examiner's search. Should the elected species be found allowable, the examiner would then move on to other species within the broader genus, the applicants are not being restricted to a single compound for patentability.

The arguments made by the applicant regarding the restriction requirement have not been found persuasive. Examiner has found no special technical feature among these compounds, and hence has found no unity of invention. Therefore this restriction is considered proper and thus made **FINAL**.

Priority

2. Acknowledgment is made of applicant's claim for domestic priority. The current application, 10/541,657, filed on March 3, 2006, is a national stage application of PCT/US04/01267, filed on January 14, 2004, which claims domestic priority to U.S. Provisional Applications 60/440,394, filed on January 14 ,2003; 60/449,829, filed on February 24, 2003; 60/453,390, filed on March 6, 2003; and 60/470,875, filed on May 14, 2003.

Specification

3. Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. Complete revision of the content of the abstract is required on a separate sheet.

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Drawings

5. The informal drawings are not of sufficient quality to permit examination. Accordingly, replacement drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to this Office action. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. Presently, Figured 4D is missing the legend for the X axis of the graphical illustration.

Applicant is given a TWO MONTH time period to submit new drawings in compliance with 37 CFR 1.81. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a). Failure to timely submit replacement drawing sheets will result in ABANDONMENT of the application.

Claim Objections

6. Claims 1-78 are objected to because of the following informalities:

Claims 1-78 are objected to for containing non-elected subject matter within the claims. In addition, several claims in their entirety no longer contain any elected subject matter. (See for example claims 4-8, 10, 62-69, 71 and 77). Applicant is supposed to proved examiner with a listing of the "correct" pending claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 9, 11-61, 70, 72-76 and 78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pyrimidine where R_1 is a hydrogen; the N-A-B-D ring is a piperidinyl ring; and Ar_1 is a phenyl, benzyl, fused phenyl or fused benzyl ring, does not reasonably provide enablement for all of the other groups listed nor any hydrates or solvates within the broad Claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (United States v. Teletronics Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See Ex parte Forman 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant*. The Applicant has demonstrated within the application how to make triazolopyrimidines and pyrazolopyrimidines. However, there is no working example of any compounds with R groups other than previously mentioned nor has applicant demonstrated any N-oxides, prodrugs, polymorphs or formulations. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However...there is no evidence that such compounds exist...the examples of the '881 patent do not produce the postulated compounds...there is...no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

2) *Unpredictability in the art*. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

The scope of "solvate" and "hydrate" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Solvates cannot be predicted and there fore are not capable of being claimed if the applicant cannot properly enable a particular solvate.

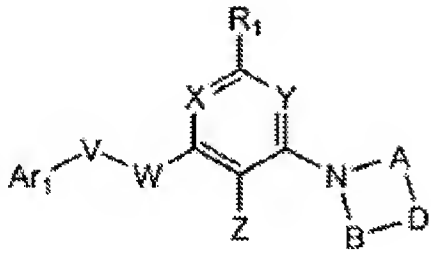
> "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal

> lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates." Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.

3) *Number of working examples*. The compound core depicted with specific substituents represents a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples of any compounds, compositions or pharmaceutically acceptable salts where the R variables were not those mentioned above in the present application.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

4) *Scope of the claims*. The scope of the claims involves all of the millions of compounds of the following formula:



thus, the scope of claims is very broad.

5) *Nature of the invention*. The present invention relates to certain 1,2,3-trisubstituted aryl and heteroaryl derivatives that are modulators of glucose metabolism. Accordingly, compounds of the present invention are useful in the prophylaxis or treatment of metabolic disorders and complications thereof, such as, diabetes and obesity.

6) *Level of skill in the art*. The artisan using Applicants invention would be a chemist with a Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compounds or compositions or treating the diseases mentioned.

Claim Rejections - 35 USC § 112, 2nd paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-3, 9, 11-61, 70, 72-76 and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The scope of “heteroaryl” and “heterocycloalkyl” requires clarification. Applicants' examples in the specification are not limiting. Applicants have not defined these terms with reasonable clarity. See definitions on p.16 of the specification. Where applicants define terms with a special meaning, they must set out the special definition with "reasonable clarity, deliberateness and precision". Note *Teleflex v. Ficosa*, 63 USPQ2d 1374; *Rexnord Corp v. Laitram Corp*. 60 USPQ2d 1851 and MPEP 2111.01.

The terms are defined with non-limiting examples making them impossible to pin down. For example, when one states C_1-C_4 alkyl, there are a small finite number of possibilities that exist in that set. One ordinarily skilled in the art realizes and understands this. However when one states, “heterocycles” optionally substituted and then provides a list of well over 50 examples and states the list is non-limiting, how can this be considered definite? One skilled in the art could instantly envision well over one hundred 100 ring systems that qualify under this broad, vague definition. Does the applicant wish to claim a thiophene or a triazolopyrimidine? Applicant must narrow such broad terminology by either eliminating such a broad definition or by inserting the specific ring systems they wish to cover into the claim themselves. These arguments also apply to definitions within the specification which contain these terms, such as “heterobicycloalkyl,” “heterobicycloalkylalkyl” or “heterocycloalkylalkyl.”

11. Claim 56 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 56 states that R18 can be a "carboxy" group. In the chemical realm, a "carboxy" group has been interpreted to be two different things. One, is a carbonyl group, or a C(O) group (see Online Merriam–Webster's dictionary: http://www.merriam-webster.com/dictionary/carboxy). The second, is a carboxylic acid group, or C(O)OH group (See the definition given at http://www.answers.com/topic/carboxy-group). Applicants are not clear as to which group they intended in the present claim. Examiner is interpreting this term "carboxy" as a carboxylic acid. However, if the applicant intended otherwise, it should clear the record so as there is no ambiguity. Appropriate correction is required.

12. Claims 78 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 78 recites the limitation "agonist compound" in claims 1, 73 or 74. There is insufficient antecedent basis for this limitation in the claim. The term "agonist compound" is not present in any of these three claims. Examiner recommends amending claim 78 to simply read, "compound". No new matter permitted. Appropriate correction is required.

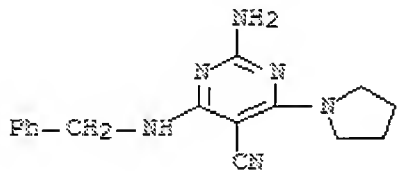
Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

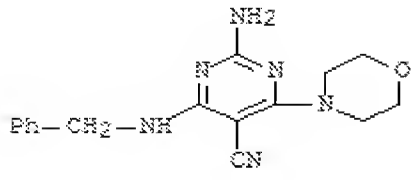
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-3, 9, 12, 14-17, 32, 39, 41, 42 and 70 are rejected under 35 U.S.C. 102(b) as being anticipated by Cocco, et. al., Journal of Heterocyclic Chemistry (2000), 37(4), 707-710. The reference teaches the following compounds as examples 4a and 4b on page 709:

RN 308356-27-6 CAPLUS
CN 5-Pyrimidinecarbonitrile, 2-amino-4-[(phenylmethyl)amino]-6-(1-pyrrolidinyl)- (CA INDEX NAME)



RN 308356-29-7 CAPLUS
CN 5-Pyrimidinecarbonitrile, 2-amino-4-(4-morpholinyl)-6-[(phenylmethyl)amino]- (CA INDEX NAME)



Whereby X and Y are N; W is a NH; V is a methylene group; Ar_1 is a phenyl ring; R_1 is an amino group; Z is a CN group; and the N-A-B-D ring is either a pyrrolidinyl ring or a morpholine ring.

Conclusion

15. Claims 1-3, 9, 11-61, 70, 72-76 and 78 are rejected.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on Mon.-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Mr. James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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